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(54) Eustatic composition for nonspecifically facilitating and amplifying the generalized homeostatic regulation and maintenance, compensation and repair in living organisms.

(57) Normal physiological function is maintained in an organism under varying kinds and degrees of stress by the action of a highly complex system of interior regulation, designed here as the Homeostatic Regulatory System (HRS). The functioning of the HRS can be facilitated and enhanced by the exogenous application of a variety of nonspecific agents, herein termed "eustatants." The administration of eustatants to an organism makes it possible to produce a state of amplified homeostasis, or "eustasia."

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EUSTATIC COMPOSITION FOR NEONSPECIFICALLY FACILITATING
AND AMPLIFYING THE GENERALIZED HOMEOSTATIC REGULATION
AND MAINTENANCE, COMPENSATION AND REPAIR IN LIVING
ORGANISMS

This invention relates to agents for nonspecifically facilitating and enhancing the normal homeostatic regulation and repair processes in living organisms. These agents are called "eustatants".

5 In living organisms, there is constant pressure from regulatory mechanisms toward metabolic stabilization, or health, and away from the pathology of injury, or disease. Thus, if injury is defined in its most inclusive sense as any forcible unbalancing of the steady state of
10 an organism, not all injury will result in disease or ill-health. Undetected injuries are constantly occurring and being corrected by the organism's internal system of metabolic regulation and preservation. This concept of internal metabolic regulation has been termed "homeostasis."

15 Homeostasis embraces the full range of physiological responses to almost all conceivable injuries, and also accounts for the continuous regulation of all routine maintenance phenomena, such as amino acid synthesis, blood pressure, neuromuscular control, respiration, excretion
20 and body temperature. What we call herein the "Homeostatic

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Regulatory System," or HRS, is an organism's inherent system of defense against disease-producing injury and its capacity for maintaining vital life functions. The HRS involves all the cells of an organism.

5 Obviously, there are limits to the capacity of the HRS to perform its function of maintaining the integrity of the living organism, i.e., the injury to the organism may be so extensive that the HRS is overwhelmed at least temporarily. In that event, specific
10 external agents--usually in the form of medications--are required in order to restore the organism to health. To minimize the occurrence of such traumas, it would be of great benefit if completely innocuous means were found for enhancing an organism's ordinary homeostatic ability
15 to maintain itself and counteract the injuries of disease and degeneration. Such means would produce a general, pervasive augmentation of normal HRS activity while, at the same time, enhancing the organism's specific capacity to respond to specific injuries.

20 Despite the immense benefit that might accrue from devising ways of promoting HRS activity, the immense complexity of the system seems up to now to have discouraged notions of finding a general stimulant to homeostasis. One fact that is clear, however, is that the
25 underlying means by which homeostatic regulation is

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modulated is the process of information transfer among the cells of the organism. As a result of advancement in the past ten to fifteen years in the understanding of the mechanism by which the cells of an organism
5 "communicate" with the one another, it has now become possible to devise a variety of external agents or agencies for producing a general rise in HRS activity with all the attendant consequences of enhanced--and appropriate--defense, repair and maintenance effects.

10 Such exogenous agents or agencies are herein termed "eustatants," the prefix "eu" indicating a betterment of ordinary homeostasis, or "eustasis"--in effect, extraordinary homeostatis. "Eustasis" can be defined simply as the catalytic amplification of normal cellular
15 communications that are involved in homeostatic regulatory processess. In order to understand how "eustatants" have been identified and how the administration of such substances can generally facilitiate and amplify the process of information transfer among cells, a brief
20 summary of current knowledge about intercellular communications is helpful.

Intercellular communication in higher animals takes place in essentially two ways. One way involves the nervous system; the other involves the endocrine system f
25 secretory cells. Information transfer in the nervous

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system occurs directly from one cell to another across intercellular junctions called synapses via chemical agents called neurotransmitters. Information transfer via the endocrine system occurs indirectly, through
 5 hormones that are disseminated throughout the organism by the circulatory systems.

Both neurotransmitters and endocrine hormones, together often called "mediators," interact with specialized sites called "receptors," on the surfaces of
 10 cells being communicated with. Mediators originate in a variety of ways, from the stimulation of certain cells by various factors in the external environment (e.g., irradiation, toxins), to metabolic processes occurring within the organism.

15 In the first step of the intercellular communications process, any specific mediator-receptor engagement at the cell surface provokes the activation of adenylate cyclase within the cell membrane. In the next step, adenylate cyclase degrades molecules of the chief energy-
 20 storage substance of cells, called adenosine triphosphate, or ATP. The removal of two of its three high-energy phosphate groups converts ATP into adenosine monophosphate, or more precisely, cyclic AMP or "cAMP." The action of
 25 cAMP on preformed but inactive enzymes in the cell, called kinases, allows those enzymes then to go forth and activate

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still other preformed but inactive enzymes and hormones in the cell whose particular functions correspond appropriately to the needs of the cell for survival and of the organism for maintenance. Those particular needs are reflected at any given moment by the messages received by the cell in the form of mediators and by the prevailing electrochemical microenvironment of the cell (and organism). Different cell types are distinguished not only by their surfaces, but by the enzymes and hormones they contain and which determine the metabolic functions that are characteristic of those cells. Thus, only certain kinds of kinase-activatable enzymes and hormones are present in cells of a particular type, and the universal cAMP will therefore cause only those specific molecules to be activated.

The kinase-activatable enzymes and hormones present in the cell are pre-formed by the cell's genome--the genes contained in the rod-like chromosomes that reside in the cell nucleus and carry the programmed genetic information that confers its biochemical (structural, compositional, functional) identity upon each cell and the parent organism. Other enzymes and hormones are produced by direct stimulation of the genome. For example, steroid hormones in most instances move directly to the genome rather than, as the peptide hormones do,

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triggering adenylate cyclase activity in the cell's
outer (plasma) membrane. Coupled with its glycoprotein
receptor site, steroid hormone travels through channels
in the cell's cytocavitary network of intracellular
5 membranes. When it arrives at the nucleus, the hormone-
receptor complex induces activity of a particular gene
whose function it is to promote the production of a
certain protein--e.g., an enzyme or other hormone-- which
represents a specific response to the mediator's hormonal
10 message.

Thus, cells generate protein responses (in the
form of enzymes and hormones) to mediator-borne messages
from outside the cell in essentially two ways, both of
which are tied to the genome. One way is via the kind of
15 mediator-receptor interaction that stimulates adenylate
cyclase-cAMP activation of enzymes and hormones that were
produced earlier in inactive form by the genome. This
mode of protein generation by activation is much faster
than the other route, in which the steroid hormone-receptor
20 site travels to the genome for direct, specific induction
of genetic activity. Thus, a differential in rate of
response to messages of different sorts represents yet
another modulatory control on homeostatic processes.

Hormone mediators need not always be involved in
25 communications with the genome. Chemical constituents

of the intracellular fluid (cytoplasm), or even from the intercellular spaces outside the cell, can induce the genome to promote the synthesis of molecules appropriate to the circumstances represented by the stimulating agent.

5 It should be clear that the essential elements of the cellular communications system are the genome and cell membranes. The latter includes the cell's surrounding plasma membranes and associated cytocavitary network of membranes inside the cell. The mechanisms by which the
10 genome and cell membranes mediate information-transfer processes in cells reveal much about the basic mechanisms of eustasis itself, and how eustatants can be employed to amplify homeostasis processes in health and disease.

The Genome

15 The genome performs two operations on the information it carries encoded in the structure of the deoxyribonucleic acid (DNA) of which its component genes are made. One function is transmission of genetic information. This is accomplished by replication of both
20 strands of the double-helical DNA during cell division (reproduction); one copy of the genome goes to each of the new cells. The other operation--transcription of genetic information--is the one that is performed during homeostatic regulatory activity. Transcription consists of the
25 transfer of information encoded in the structure of DNA to

the structure of a messenger, ribonucleic acid (mRNA). Genetic information now encoded in the structure of the mRNA is finally translated into the assembly of sequences of amino acids that constitute the proteins (e.g., enzymes, hormones) that are needed by the cell for various life-sustaining purposes.

The human genome is known to contain between 30,000 and 100,000 genes whose structures--informational contents--are spelled out in the sequences of part of the six billion nucleotide pairs that constitute human DNA. Stretched out in a long, double-helical strand, that much DNA would measure two meters (more than six feet) in length. Not only must all of that chemically coded information be contained within a volume of less than ten one-millionths of a meter in diameter--the cell nucleus--but the DNA must be able there both to replicate itself with a high degree of fidelity and to transcribe the information it bears into the structure of messenger RNA. The difficult feat of packing so much information into so small a space is made possible by a trebled coiling of the genetic material on itself. First, a stretch of DNA double helix is wound around little balls of histone protein at intervals of every 200 nucleotides, with about 140 nucleotides wrapping each histone ball. That "string of beads" is then coiled into another coil with about six of the

beads in every turn. Finally, that coiled coil is looped once more on itself and attached to a protein scaffold-- the entire assembly constituting a chromosome, one of the 46 in the human cell nucleus.

5 In actuality, only about 1/200th of the DNA of the genome, or roughly 30 million nucleotide pairs out of the six billion in the entire genome, actually code for protein synthesis. Presumably, the genetically inert regions of the DNA function at least partly to permit the intricate
10 packing described above. According to this view, genetically active regions are located where mediators and other inducing substances can reach them most easily. Presumably, also, there is some priority to the arrangement of even those active regions, the most vital ones securing
15 the most accessible positions, with regions of lesser value to the cell's (organism's) maintenance and survival occupying positions that either are more difficult to reach or are least unlikely to become occluded by injury or accident in the course of repeated replication of the
20 genome.

 In the context of eustasis, then, agents or agencies which would facilitate intercellular communications via action on the genome would necessarily do so by enhancing the transcription of genetic information from
25 DNA to mRNA. This might be done by producing a reversible

"relaxation" of some sort in the genome so that its constituent genes would become more easily assessible for transcription.

Cell Membranes

- 5 According to the "fluid mosaic model," the plasma membrane which surrounds the cell can be thought of as a sandwich of three layers. The top layer makes contact with the cell's external environment through the substance of the intercellular space outside. The bottom layer forms
- 10 an interface with the cell's cytoplasm and cytocavitary network inside. Each outer layer is composed of electrically charged polar head groups of phospholipid molecules. The intermediate layer consists of non-polar fatty acid chains of the phospholipids.
- 15 Also inside the sandwich are scattered lumps of globular proteins that sometimes protrude through one or both outer layers. In addition, glycosides--complex carbohydrates--are attached to some of the lipids (as glycolipids) and to some of the proteins (as glycoproteins).
- 20 The glycosides crop out of both surfaces, on the exterior and the interior, of the cell's plasma membrane. Those protuberances of protein mark regions of the cell's receptor sites. The resultant structure is, thus, a mosaic of essentially globular proteins (and glycoside complexes) in
- 25 a viscous fluid matrix of lipid (fatty substance).

That structure serves many purposes. For example, cell membranes can act as pumps for actively transporting certain substances in and out of the cell or various cell structures. They also participate in the charge-transfer interactions among species of molecules and ions in the cellular environment. The cell membrane also serves as a supporting matrix for enzymes (e.g., adenylate cyclase) and their actions. Its plasticity enables the plasmalemma to engulf substances in the surrounding milieu and imbibe them for use inside the cell and also to pass internal packets of cell-produced substances for excretion into the intercellular space.

All those functions and others are intrinsically involved in cellular communications and, so, are essential contributors to homeostatic regulation. A central aspect of the present invention, then, is the discovery how membrane and genomic function might be enhanced to improve cellular communications.

It is an object of the present invention to provide a method for facilitating and amplifying the normal activity of the Homeostatic Regulatory System (HRS) of an organism, thereby promoting the optimal functioning thereof.

It is another object of the present invention to provide a method for facilitating and amplifying the normal activity of the HRS of a living organism which does not

produce deleterious side effects.

It is yet another object of the present invention to provide a method for promoting the generalized optimal physiological functioning of an organism within its normal range while simultaneously enhancing the organism's specific responses to specific injuries.

It is a further object of the present invention to identify a new class of pharmacologic, nutritional, therapeutic and tonic agents, herein called "eustatants."

It is a still further object of the present invention to provide formulations of eustatants which can be administered to humans and other living organisms.

These and other objects of the invention will be apparent from the description and the examples hereinafter set forth.

THE INVENTION

The method of the present invention and the eustatic agents used therein accomplish the aforementioned objects by augmenting aspects of the normal activity of the basic cellular components of the intercellular communications system--the genome and the cell membranes. In this connection several circumstantial factors influencing the activity of both genome and cell membranes can be identified as being involved in the enhancement of cellular communications, including:

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1. Accessibility to cell membranes by mediators and other "informational substances";
2. Availability of specificity mechanisms, such as unobstructed receptor sites and matching mediator-receptor encounters;
3. Penetrability of cells by substances moving through the plasma membrane;
4. Conduction of informational substances to appropriate cellular organelles, including the nucleus;
5. Expressability of the genome as determined partly by the exposure of genes to informational substances.

In operational terms, those communications-related factors suggest the following means of functional facilitation of each one, respectively:

1. Facilitated chemical interaction among cells by either increased flow-rate of chemical species or an increased permeability of the intercellular substance through which mediators and other components of the cells' microenvironment must pass to reach cell membranes, or both;
2. Open receptor sites and increases probability of encounters with matching mediators and, perhaps, increased rate of receptor site

replacement;

3. Increased plasma membrane activity, especially permeability and pinocytosis;
4. Increased electrochemical activity of the cytocavitary network, including the nuclear envelope;
5. A relaxation of some sort in the genome, perhaps by a change in the nuclear membrane's barrier potential or a reversible unwinding of the DNA, or both, for greater interactions between the genome and mediators and other cytoplasmic constituents.

Achieving any one of the above effects on the inter-cellular and intracellular environment should produce signs of at least mild enhancement, or amplification, of homeostatic regulation, or eustasis. Achieving several or all of them should produce marked or even extraordinary eustatic consequences.

Agents and agencies have been discovered which may promote these effects. These agents and agencies and the suggested mechanism by which they work are described in detail below.

Pseudoaqueous Substances

The category of pseudoaqueous substances encompasses dimethyl sulfoxide (DMSO) and other compounds having

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a strong solvent action through living tissue which have electrochemical properties, such as dielectric constant and charge transfer capability, closely resembling those of water. Other compounds in this group would include the toxic chemical dimethyl formamide (DMF) and non-toxic ethylene cyclic carbonate and N-methyl pyrrolidinone.

In the context of cellular communications, the powerful solvent action of these compounds serves to flush nutrients, ions and various informational substances throughout the organism to and often through cell membranes, even to the genome. They may also affect membrane function, modifying the electrochemical microenvironment of those structures by facilitating the rate and degree of exposure of membranes to both charged and uncharged chemical species from throughout the organism, and altering the composition of the membrane-bound chemical population. Pseudoaqueous eustatants may also act by clearing blocked receptor sites and facilitating mediator-receptor match-ups.

Metal Ions

Certain metal ions, preferably divalent metal cations, have a selective affinity for reiterative nucleotide sequences in the DNA molecule and, when bound there, cause a reversible unwinding of the double helix. This action may be expected to increase the exposure of the genome to constituents of its immediate cellular environment

and, in that way, presumably facilitate optimal genetic expression. In addition, divalent metal cations are known to bind strongly to cell membranes, thereby altering their structure and function. Also, the mere presence of these
5 in the vicinity of membranes will alter their electrochemical microenvironment, influencing membrane function in that way as well.

An additional role for divalent cations to play in eustatic (and homeostatic) processes, which is hereinafter
10 discussed in greater detail, involves the requirement for them in the depolymerization of hyaluronic acid in interstitial regions by reducing agents, an effect that increases access to cell surfaces.

Ions that have been chiefly associated with these
15 effects and which are apparently tolerated by cells (at least in small concentrations) without significant irreversible toxicity include zinc, manganese, iron (the ferrous ion), copper (the cuprous ion) and trivalent chromium (the latter two in much lower concentrations than the former
20 because of their greater toxicity).

Glycosaminoglycans

One of the most common and visible of all corrective, i.e., homeostatic, responses to injury is the inflammatory process. The acute inflammatory response is highly complex
25 but can be reduced essentially to two independent events.

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Both represent aspects of cellular communications. One event is the accumulation of scavenger cells--leukocytes--that are summoned to the site of injury by chemical messages sent out by the injured cells. The other event consists of an alteration in the permeability of cells and tissues. This creates freer movement by leukocytes and other corrective substances--e.g., antibodies--into the injured region, there to perform their defensive/reparative functions. Clearly, the inducement of the modified permeability of cells and tissues that occurs as part of the inflammatory process without also inducing the other aspects of the inflammatory process--e.g., the accumulation of leukocytes--would have eustatic consequences, i.e., an amplifying effect on intercellular communications.

The suggestion that such a result would be achieved in an organism by the administration of glycosaminoglycans has been garnered from published reports of experiments performed in the 1950's. Given the ubiquity of the classic homeostatic process of wound healing and the suggestion that glycosaminoglycans play a role in it, it has been possible to identify one glycosaminoglycan of particular importance--hyaluronic acid. Not only is hyaluronic acid present in appreciable quantities in all cartilage and in more other tissues than any other glycosaminoglycan, it is

an important constituent of the pervasive intercellular matrix. The following known facts are pertinent to the participation of hyaluronic acid in the facilitation of cellular communications.

- 5 1. Like other glycosaminoglycans, hyaluronic acid exists naturally as a polymer, a long chain of repeating disaccharide units (a glucuronic acid and a glucosamine) linked covalently (strongly) to a polypeptide
10 (protein-like) backbone as a "proteoglycan"-- a class of substances that forms the ground substance in the extracellular matrix of connective tissue.
- 15 2. The hyaluronic acid polymer carries a net negative electrical charge and, thus is classed as an anion, or more precisely, a polyanion.
- 20 3. In its native state as a sticky gel between cells, the hyaluronic acid portion of the proteoglycan matrix is a relatively large polymer with a molecular weight of around 10 million--
too large, as such, to enter cells.
- 25 4. The hyaluronic acid component of intercellular proteoglycans depolymerizes into lower molecular-weight fragments (that are small enough to enter cells) by the action of enzymes of two

kinds--certain glycosidases and proteases that degrade the carbohydrate and polypeptide parts of the proteoglycan, respectively.

- 5 5. Proteoglycans are large polyvalent anions which so tightly bind cations, such as metal ions, that they appear uncharged. Proteoglycans tend to aggregate, and this tendency is enhanced by polyvalent cations such as Ca^{2+} .
10 Larger chains, such as that of hyaluronic acid, coil in a relatively random way and therefore may occupy a volume largely filled with solvent water to which small molecules or ions have access, but from which larger molecules may be excluded. This volume is the domain of the
15 polysaccharide. Degraded glycosaminoglycans are excreted in the urine, their observed size suggesting that they have been partially degraded by glycosidases. Human adults degrade about 250 milligrams of proteoglycans per day,
20 but since normal urine contains only a few milligrams of the partially degraded glycosaminoglycans, considerable degradation must occur in the tissues.
- 25 6. Hyaluronic acid is constantly being formed in tissues by the action of enzymes called

transferases. It is depolymerized both enzymatically, by certain glycosidases (especially hyaluronidase) and non-enzymatically by oxidation-reduction systems and by ionizing radiation.

From the foregoing facts, the mechanisms by which hyaluronic acid, the cement substance in the intercellular matrix contributes to its own degradation, producing the necessary loosening of the junctional zones for the percolation of substances to cell surfaces, become evident. In addition, a means by which hyaluronic acid can play a role in the function of the genome is suggested, namely by carrying into cells DNA-unwinding metal cations. Thus, this glycosaminoglycan undoubtedly performs not just one but at least two key functions in the facilitation of cellular communications during homeostatic (and eustatic) regulatory activity.

The following scenario describes the way hyaluronic acid acts as a native homeostatant or an administered eustatant.

Low molecular-weight fragments of hyaluronic acid--either the native stuff degraded naturally in tissues or administered in the form of powdered cartilage (or some other tissue source)--assemble into separate small domains or zones of a gel. These hyaluronic gel-cells may contain

nutrients, small informational substances, water and positively charged metal ions. The metal ions, as indicated earlier, can act as homeostatants or eustatants, themselves. If the ordinarily negatively-charged hyaluronic acid gel-cell has bound to a positively charged metal ion, the combination is electrically neutralized and may be small enough to enter a cell, presumably through an engulfment process as pinocytosis.

The presence of hyaluronic acid inside the cell can then induce the genome to promote the synthesis of hyaluronidase, the hydrolytic enzyme whose specific substrate is hyaluronic acid. That enzyme would then depolymerize the gel-cell, causing release of its contents of water, nutrients and metal ions. The metal ions would bind to DNA and produce a reversible unwinding of the genome, exposing it more fully to whatever informational substances were either already present in the cytoplasm or carried in by the hyaluronic acid gel-cell.

Both the hyaluronidase, synthesized under the direction of the genome in response to the presence of hyaluronic acid, and the fragments of gel-cells that the enzyme has degraded may then be excreted from the cell into the extracellular space. There the enzyme can continue its depolymerization of hyaluronic acid in the cement, producing a further loosening of the matrix for enhanced percolation

of substances to cell surfaces. Some of those substances may be gel-cells newly generated by the action of the enzyme. And, of course, the excreted fragments of gel-cells can reaggregate as hyaluronic acid--along with the polymer synthesized by transferases--in the proteoglycan matrix, restoring the cement for the process to begin again.

It should be clear that the above process is cyclic, an autocatalytic amplification effect. Thus, one substance (hyaluronic acid) catalyzes the production of another (hyaluronidase) that catalyzes the generation of a form of the first substance (the gel-cell) that can re-enter the cycle, amplifying the overall reaction sequence.

This process undoubtedly occurs at a very low rate constantly in organisms, contributing minutely but continuously to homeostatic regulatory processes that maintain the organism's statistical edge against perpetual injury and imbalances in maintenance requirements for health and survival. Exogenous administration of hyaluronic acid will increase the rate of the process, thus producing the greater permeability of the intercellular substance. In addition, the hyaluronic gel-cells serve to carry metal ions to the genome which bind to the DNA and produce the reversible unwinding of the genome previously discussed.

The preferred glycosaminoglycan for administration as a eustatant is hyaluronic acid, which, can be obtained

in quite pure form from the vitreous body of the eye and from the placenta and umbilical cord. Alternatives include mixtures of hyaluronic acid and the sulfated chondroitins which may be derived from deproteinated cartilage, and mixtures of the hyaluronic acid amino sugar and sugar acid glycosidic components -- N-acetyl D-glucosamine and D-glucuronic acid, respectively -- which may be derived from deproteinated chitin.

Non-Toxic Saponin Glycosides

Glycoside synthesis goes on in all living cells, plant and animal alike. Glycosides are derived from simple sugars -- monosaccharides -- from which each acquires its generic name. Thus, a glycoside that is derived from the monosaccharide glucose is a glucoside, one from galactose a galactoside, from fructose a fructoside, etc. Moreover, many biologically important glycosides consist of modified monosaccharides; these include the sugar acids, amino sugars and deoxysugars. For example, modification of glucose by oxidation produces the important sugar acid glucuronic acid that plays a key role in many detoxification reactions. Another well-known sugar acid is L-xyloascorbic acid, or vitamin C. Among the amino sugars, the most important and widespread are the glucosamines, galactosamines and sialic acids, particularly neuraminic acid. And, of course, the deoxysugar deoxyribose is a key structural constituent of

the genetic material, deoxyribonucleic acid.

Many glycosides contain non-carbohydrate components, most often alcohols, phenols and sterols. Examples of these are to be found among spices, vegetable dyes and
5 drugs, including the well-known "cardiac glycosides," digitoxin and ouabain, both steroid-containing saponin glycosides. Finally, glycosides rarely occur by themselves in nature, but are linked together as disaccharides (e.g., maltose, consisting of two glucoses; lactose, a glucose
10 and a galactose, sucrose, a glucose and a fructose) and as small sugar polymers, called oligosaccharides, and larger sugar polymers, called polysaccharides. Nearly all glycosides in higher organisms are attached to proteins and lipids as glycoproteins (and proteoglycans) and glycolipids,
15 respectively, both of which abound on the surface of cell membranes.

The single property of glycosides that, more than any other, both determines and mediates their role in intercellular communications is their selective affinity
20 for one another. The chief site for this sort of glycosidic activity is the cell surface.

The outer surface of the cell membrane can be thought of as a smooth lawn of phospholipids with a lot of glycosidic "weeds" growing out of it. These glycoproteins and glycolipids form what is called a "glycocalyx"
25

over the cell surface, which may sometimes actually interfere with mediator-receptor site interactions. In its positive role, however, the qualitative composition of the glycosidic components of the glycocalyx is thought
5 to give each cell type its characteristic identity.

The patterns of glycosides on cell surfaces serve as binding sites for a variety of substances, particularly other glycosides. For example, cardiac glycosides -- the saponins digitoxin, ouabain and phlorhizin -- bind tightly
10 to the glycocalyx of the cardiac cell and interfere with ion and energy transfer across its membrane. In small doses, this is a useful affect for heart problems; in higher doses, the effect is extremely toxic.

The binding of substances to the surfaces of cells
15 produces a variety of important consequences:

1. Cardiac glycosides interfere with the energy system that drives the membrane's active ion-transport system;
2. Glycoside-coated infectious organisms, such
20 as mycoplasma, and glycoprotein antigens, such as CEA, cause cells to clump together;
3. Protein lectins and glycoside saponins, such as ouabain, affect cell-cell recognition and even induce cell division;
- 25 4. Antibodies initiate the pinocytosis of the

membrane components by some as yet unknown mechanism that is speculated to be of crucial importance in processes of cell differentiation;

- 5 5. Mediators initiate the activation of the adeny-
late cyclase-cAMP sequence of enzyme activation;
6. Even glycosaminoglycans (e.g., from the inter-
cellular matrix), by their natural glycosidic
affinity for various compositions of the
glycocalyx, must produce important effects on
10 cell functions, if only by the changes they
cause -- as, clearly, do all of the other agents
just mentioned -- in the electrochemical micro-
environment of the cell's sole communicative
link with its exterior environment, the plasma-
15 lemma.

From the foregoing, a picture of how the eustatically
effective botanical glycosides perform their functions can
now be drawn. It is worthy of note at the outset that the
particular glycosides in question are saponins, a group of
20 carbohydrates that have demonstrated their affinity for cell
membranes without question in their actions as cardiac glyco-
sides. It is clear, however, that there are important
distinctions between the eustatic saponins and their cardiac-
affecting relatives; the plant saponin glycosides that have
25 shown unequivocal eustatic effects have also shown -- unlike

the cardiac saponins -- extremely low toxicity or none at all. One property the two kinds of saponins clearly do share, however, is their affinity for cell surfaces, and this is presumably how the eustatic effects are initiated.

5 Several of these effects seem likely.

A primary and ubiquitous effect of membrane-bound eustatic glycosides, of course, would be to modify the electrochemical microenvironment of the cell membrane, perhaps leading to subtle alterations in its structure and
10 function and, hence, the facilitation of its communicational -- and homeostatic -- activity.

Second, eustatic glycosides binding to the plasma-lemma may activate the adenylate cyclase chain of reactions leading to the activation of pre-formed but inactive enzymes
15 inside the cell. These enzymes can act inside the cell or be excreted into the intercellular matrix.

The third major effect of plasmalemma-bound eustatic glycosides may be the triggering of endocytotic activity (pinocytosis and phagocytosis). This would carry the
20 glycosides into the cell where their presence could initiate both the induction of genetic neosynthesis of glycosidases of various sorts and the activation of latent glycosidases liberated by lysosomes. Again, these enzymes could act
25 both within the cell and, after excretion, in the inter-cellular matrix.

Outside the cell, glycosidases could perform a debridement of the glycocalyx, clearing receptor sites of occluding glycosides for enhanced access by mediators. Other glycosidases -- glucosaminidases, lysozyme and
5 hyaluronidase -- could depolymerize glycosaminoglycans in the matrix, loosening the intercellular substance and increasing thereby the flow to the plasmalemma of nutrients, water and informational substances.

The latter action would, of course, generate
10 hyaluronic acid gel-cells. These might bind to the glycocalyx and, themselves, trigger pinocytosis, thereby gaining entry to the cell, contents and all. Or other influences may initiate generalized endocytosis, producing the same effects.

15 Whatever the mechanism or mechanisms, it is clear that the result is a dynamic flux of cellular activity surrounding the binding and movement of glycosides and glycosaminoglycans onto and across cell boundaries, with all of the attendant consequences. The oscillations of these
20 radiating phenomena would be miniscule -- virtually undetectable, because they would take place on the level of only a few molecules (of glycosides, glycosaminoglycans, metal ion-complexes, nutrients and enzymes) at a time. Nevertheless, even these slight effects would be calculated to
25 result in a significant shift of the homeostatic balance

toward optimal physiological conditions in the organism.

Several kinds of eustatic glycosides have been identified. The most potent, least toxic and broadest ranging in effects are six saponin panaxosides and nine
5 saponin eleutherosides, all derived from the Araliaceae family of plants of which Eleutherococcus senticosus and Panax ginseng are members.

Reducing Agents

The eustatic function of these substances seems
10 to be limited initially to their known ability to depolymerize intercellular hyaluronic acid, but expands to include all of the consequent effect of that action, as described in the section above on glycosaminoglycans.

Reducing eustatants include vitamin C (ascorbic
15 acid), the amino acid cysteine, dihydroxymaleate, the inactive form of the papaya enzyme papain and other possessors of reducing thiol groups.

Chemical Sources of Molecular Oxygen

Both molecular oxygen and divalent metal cations
20 are required for the depolymerization of hyaluronic acid in the intercellular matrix by various reducing substances, such as those mentioned above. The effect of these adjunctive eustatants would thus be essentially the same as that of reducing agents. It should be noted, however, that
25 while their eustatic action is properly described as

adjunctive, for all practical purposes chemical sources of molecular oxygen -- indeed, molecular oxygen, itself -- can be expected to act, seemingly independently, as true eustatants because of the constant presence in tissues
5 of endogenous reducing agents and metal ions that coordinate with molecular oxygen for their eustatic action.

Hydrogen peroxide is the most obvious, least toxic and cheapest example of a chemical source of molecular oxygen (actually, it is a source of atomic oxygen, but two
10 such units combine readily in tissue into the molecular form). Another source would be the reduction in tissues of NAD (nicotinamide adenine dinucleotide) with water to $1/2O_2 + NADH$.

Mild Proteases

15 In addition to the role cited above for papain as a thiol-bearing reducing agent, proteases participate in eustatic processes much as glycosidases do, by splitting complexes that glycosaminoglycans and glycosides make with proteins, setting in train the cascade of reactions initiated by those carbohydrates in the free, depolymerized
20 state.

Mild proteases for which eustatic-type of action has already been documented are the pineapple enzyme, bromelain, and the papaya enzyme, papain -- in both active
25 and inactive forms.

Combining Eustatic Compositions

Certain of the eustatic compositions disclosed herein will have cooperative, synergistic effects when combined. In the discussion of glycosaminoglycans, it was noted that hyaluronic acid gel-cells serve to carry metal ions to the genome which bind to the DNA and produce the reversible unwinding of the genome previously discussed. Exogenous administration of glycosaminoglycans, particularly hyaluronic acid, and metal ions will result in a greater incidence of gel-cell encapsulated metal ions passing through the cell membrane, contributing to a greater permeability of the intercellular substance and a greater occurrence of the reversible unwinding of the genome induced by metal ions.

It was also noted in the discussion of chemical sources of molecular oxygen that both molecular oxygen and metal cations are required for the depolymerization of hyaluronic acid in the intercellular matrix by reducing agents such as ascorbic acid. A greater concentration of all of these eustatants would produce the beneficial loosening of the intercellular substance. Moreover, the addition of glycosaminoglycans, such as hyaluronic acid should further amplify the loosening effect, as well as the carriage of metal ions to the genome.

Formulations of Eustatic Compositions

Representatives of each of the categories of eustatic compositions discussed above can be rationally formulated--with the addition of certain supportive agents--
5 into at least three general classes of preparations for use as pharmacological and/or nutritional, therapeutic, prophylactic and tonic preparations.

The general formulation is herein designated "EU-PAN," suggesting its capacity to promote eustatis (EU-) over a very wide range (-PAN) of physiological states and conditions. The eustatic formulations whose carbohydrate component consists principally of hyaluronic acid, obtainable from animal sources such as deproteinated cartilage, the vitreous body of the eye, the umbilical cord and the
15 placenta, is generally designated, EU-PAN A, and is intended for use primarily as a pharmaceutical and secondarily as a nutritional supplement. The parallel formulation whose carbohydrate component consists of the non-toxic saponin glycosides derived from Eleutherococcus Senticossus
20 (Siberian ginseng) or Panax ginseng, is generally designated "EU-PAN B," and is intended to be applied primarily as a nutritional supplement although it may also be used as a pharmaceutical.

A third general formulation, "EU-PAN C," is similar
25 to EU-PAN A in that it involves the use of hyaluronic acid

glycoside components as the carbohydrate ingredient --
 in this instance, a mixture of N-acetyl D-glucosamine
 and D-glucuronic acid. EU-PAN C may also be applied as
 a pharmaceutical, but is primarily intended for use as a
 5 nutritional supplement.

Following are examples of formulations of the
 three forms of EU-PAN with acceptable ranges and preferred
 amounts of constituents indicated for daily administration
 to a human being. These examples, and the suggested forms
 10 of administration which follow, are not intended to be
 limiting, but rather illustrative of approaches that may
 be taken and, of course, which may be varied in accordance
 with the spirit and scope of this invention.

Example 1 (EU-PAN A):

15		<u>Range</u>	<u>Preferred</u>
	1. Hyaluronic acid	(500mg.-10g.)	Any amount within range
	2. Polyvalent metal cations		
	a. zinc	(15mg.-30mg.)	30mg.
	b. copper (cuprous)	(1mg.-2mg.)	2mg.
20	3. Ascorbic acid	(500mg.-3g)	2g
	4. Bromelain	(50mg.-150mg.)	100mg.
	5. Supportive Base		
	a. ribonucleic acid	(200mg.-600mg.)	400mg.
	b. inosital	(100mg.-600mg.)	250mg.
25	c. pyridoxine	(100mg.-500mg.)	200mg.

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		<u>Range</u>	<u>Preferred</u>
	d. B-complex	(standard)	-
	e. dolomite (calcium and magnesium)	(standard)	-
5	f. superoxide dismutase (SOD)	(10 μ g.-100 μ g.)	50 μ g.
	g. nicotinamide	(500mg.-3g)	2g.

In the preferred formula for EU-PAN A above, the constituent amount of hyaluronic acid may be obtained in almost pure form from animal sources such as the vitreous body of the eye, the umbilical cord and the placenta. The other constituents are commercially available. The above is a dry mixture suitable for administration as such, or encapsulated, or compacted into tablet form. The size and number of such capsules or pills to be conveniently administered will of course depend upon the amounts of constituents used. This example may optionally include nicotinamide adenine dinucleotide phosphate (NADP) as a chemical source of molecular oxygen and the polyvalent metal cations manganese, iron (ferrous) and chromium in the following amounts:

		<u>Range</u>	<u>Preferred</u>
	a. manganese	(4mg.-30mg.)	10mg.
	b. iron (ferrous)	(15mg.-30mg.)	30mg.
25	c. chromium	(100mg.-200 μ g.)	200 μ g.

Example 2 (EU-PAN A):

		<u>Range</u>	<u>Preferred</u>
	1. Hyaluronic acid and sulfated chondroitins	(500mg.-10g.)	Any amount within range
5	2. Metal ions	(Same as Example 1)	
	3. Ascorbid acid	(Same as Example 1)	
	4. Bromelain or Papain	(Same as Example 1) (30mg.-100mg.)	Any amount within range
10	5. Supportive base	(Same as Example 1)	

In this example of EU-PAN A, the constituent amount of hyaluronic acid and sulfated chondroitins may be obtained from deproteinated cartilage. The optional ingredients are the same as for Example 1.

15 Example 3 (EU-PAN A):

		<u>Range</u>	<u>Preferred</u>
	1. Hyaluronic acid or Hyaluronic acid and sulfated chondroitins	(Same as Example 1) (Same as Example 2)	
20	2. Metal ions	(Same as Example 1)	
	3. Ascorbic acid	(Same as Example 1)	
	4. Bromelain or Papain	(Same as Example 1) (Same as Example 1)	
	5. Supportive base	(Same as Example 1)	
25	6. N-methyl pyrrolidinone	-	-

This example is the preferred liquid form of EU-PAN A which benefits from the addition of the pseudoaqueous eustatant N-methyl pyrrolidinone. Alternatives to methyl pyrrolidinone would include ethylene carbonate or hydrogen peroxide.

Example 4 (EU-PAN B):

	<u>Range</u>	<u>Preferred</u>
1. Eleutherosides	(500mg.-10g.)	2g.
2. Polyvalent metal cations	(Same as Example 1)	
3. Ascorbic acid	(Same as Example 1)	
4. Bromelain	(Same as Example 1)	
5. Supportive Base	(Same as Example 1)	

In the above example, the constituent amount of eleutherosides may be obtained from Siberian ginseng (Eleutherococcus senticosus). This composition may optionally include the polyvalent metal cations manganese, iron (ferrous) and chromium in the following amounts.

	<u>Range</u>	<u>Preferred</u>
a. manganese	(4mg.-30mg.)	10mg.
b. iron (ferrous)	(15mg.-30mg.)	30mg.
c. chromium	(100 μ g.-200 μ g.)	200 μ g.

Example 4 is a dry mixture, suitable for administration as such, or encapsulated, or compacted into tablet form.

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Example 5 (EU-PAN B):

	<u>Range</u>	<u>Preferred</u>
1. Panaxosides	(500mg.-10g.)	2g.
2. Polyvalent metal cations	(Same as Example 1)	
5 3. Ascorbic acid	(Same as Example 1)	
4. Bromelain	(Same as Example 1)	
5. Supportive Base	(Same as Example 1)	

The constituent amount of panaxosides in this example may be derived from Panax ginseng. The optional ingredients are the same as in Example 4.

Example 6 (EU-PAN B):

	<u>Range</u>	<u>Preferred</u>
1. Eleutherosides or Panaxosides	(Same as Example 4) (Same as Example 5)	
15 2. Polyvalent metal cations	(Same as Example 1)	
3. Ascorbic acid	(Same as Example 1)	
4. Bromelain	(Same as Example 1)	
5. Supportive Base	(Same as Example 1)	
6. Water	-	-

The preferred liquid form of EU-PAN B above employs water in any convenient amount as the pseudoaqueous component.

Example 7 (EU-PAN C):

		<u>Range</u>	<u>Preferred</u>
	1. N-acetyl D-glucosamine and D-glucuronic acid	(500mg.-10g.)	Any amount within range
5	2. Polyvalent metal cations	(Same as Example 1)	
	3. Ascorbic acid	(Same as Example 1)	
	4. Bromelain	(Same as Example 1)	
	5. Supportive Base	(Same as Example 1)	

The glycosaminoglycans of EU-PAN C, namely, N-acetyl
 10 D-glucosamine and D-glucuronic acid, may be obtained in
 relatively pure form from chemical suppliers. Optional
 ingredients are the same as for Example 1. The above is
 a dry mixture suitable for administration as such, or
 encapsulated, or compacted into tablet form. The preferred
 15 liquid form of EU-PAN C, like that of EU-PAN A, employs
 N-methyl pyrrolidinone as its pseudoaqueous eustant.

Supportive Base

While not themselves eustatic agents, the items listed
 in the "Supportive Base" component of the three kinds of
 20 EU-PAN formulations do, as their designation suggests,
 have the capacity to contribute to eustatic processes by
 working in concert with eustatants.

Ribonucleic acid, for example, is synthesized -- and
 its nucleotide components thus consumed -- in eustatic
 25 activity that promotes the synthesis of protein enzymes and

hormones. Supplementing eustatant preparations with an RNA "digest" thus creates a ready surplus of ribonucleotides over endogenous sources. (Amino acid supplementation might similarly be justified to account for elevated levels of protein synthesis in eustasis, but this is probably provided for adequately by the normal diet.)

Inositol is suggested because of the connection this B-complex substance has with glycoside activity (notably in the synthesis of growth-promoting factors in plants); pyridoxine (vitamin B-6) is associated with zinc utilization; nicotinamide (vitamine B-3) would augment endogenous reserves to promote the synthesis of nicotinamide adenine dinucleotide (a potential route to molecular oxygen in the tissues).

B-complex would support the utilization of these B vitamins.

Dolomite, on the other hand, might be argued to act as a eustatant, itself, serving as it does as a convenient supplemental source of the polyvalent cations of calcium and magnesium. Those ions may, in fact, contribute to eustatic activity as other divalent cations do. However, a better established rational for including dolomite as a eustatant-supportive substance is that the divalent calcium ion is a key factor in membrane function, particularly as it pertains to information transfer in cellular communications.

Superoxide dismutase (SOD) might also be considered more properly classified as a source of molecular oxygen

because the enzyme's action on the superoxide anion produces hydrogen peroxide and oxygen in the process. The direct utilization of those products of SOD catalysis in tissues to assist in the promotion of eustasis by the action of reducing agents and metallic ions on hyaluronic acid, however, is only speculative at this point.

Administrations

As wide a variety of administratable forms of the three EU-PANS exists as there are possible routes of administration. All should produce effective results, inasmuch as eustatants act systemically and do not select target specific organs or tissues. At the same time, certain forms of the EU-PANS should produce better results than others because of a more direct (and concentrated) exposure of a particular affected part of the organism requiring regulatory maintenance of one sort or another. Thus, a pharmacologic EU-PAN (type A, B or C) administered in the form of a suppository would be useful in a rectal conditions (such as hemorrhoids), droplet EU-PAN in eye, ear and nose conditions, a cream or ointment EU-PAN in cases of epidermal eruptions and trauma (cuts, burns, bruises), etc. The fluid form of EU-PAN should be a particularly effective means of administering the eustatant formulation because the pseudoaqueous component would not only itself promote eustasis systemically but

would serve, also, as a carrier of the mixture rapidly throughout the entire organism (as DMSO has shown the capacity to do). The above forms of administration can be used to improve epidermal conditions, and led to healthier skin, hair and nails.

The nutritional EU-PAN (A, B or C) could likewise, be taken in capsule, tablet or liquid form preferably, in a flavored (non citric) beverage of some sort -- or fabricated into a food product, such as a nutrient bar.

This invention has been described in terms of specific embodiments set forth in detail, but it should be understood that these are by way of illustration only and that the invention is not necessarily limited thereto. Modifications and variations will be apparent from this disclosure and may be resorted to without departing from the spirit of this invention, as those skilled in the art will readily understand. Accordingly such variations and modifications of the disclosed invention are considered to be within the purview and scope of this invention and the following claims.

CLAIMS

1. Eustatic ^{composition/} [for nonspecifically facilitating
and amplifying the generalized homeostatic regulation
and maintenance, compensation and repair in a living
5 organism
comprising a
polyvalent metal ion and a carbohydrate, for promoting
depolymerization of intercellular hyaluronic acid and
formation of hyaluronic acid gel-cells, selected from the
10 group consisting of a glycosaminoglycan and a non-toxic
saponin glycoside.
2. The composition of claim 1 which
further comprises at least one member selected
from the group consisting of a pseudoaqueous substance
15 having a strong solvent action through living tissue, a
reducing agent for depolymerizing intercellular hyaluronic
acid in the presence of a polyvalent metal ion and mole-
cular oxygen, a chemical source of molecular oxygen for
reaction with a polyvalent metal ion and said reducing
20 agent in the depolymerization of intercellular hyaluronic
acid, and a mild pro
3. The composition of claim 2 wherein
said polyvalent metal ion comprises at
least one member selected from the group
25 consisting of divalent zinc, manganese, iron

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(the ferrous ion) and copper (the cuprous ion) and trivalent chromium;

5 said glycosaminoglycan comprises at least one member selected from the group consisting of hyaluronic acid, a mixture of hyaluronic acid and sulfated chondroitins and a mixture of N-acetyl D-glucosamine and D-glucuronic acid;

 said non-toxic saponin glycoside comprises at least one member selected from the group consisting of panaxosides and eleutherosides;

15 said pseudoaqueous substance comprises at least one member selected from the group consisting of dimethyl sulfoxide (DMSO), ethylene cyclic carbonate and N-methyl pyrrolidinone;

 said reducing agent comprises at least one member selected from the group consisting of ascorbic acid, cysteine and dihydroxymaleate;

20 said chemical source of molecular oxygen comprises at least one member selected from the group consisting of hydrogen peroxide and nicotinamide adenine dinucleotide phosphate (NADP); and

25 said mild protease comprises at least one

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member selected from the group consisting of bromelain and papain.

4. The composition of claim 3 wherein

said polyvalent metal ion includes zinc or copper (cuprous);

said carbohydrate is a glycosaminoglycan and said glycosaminoglycan includes hyaluronic acid;

said eustatic composition includes a reducing agent and said reducing agent includes ascorbic acid; and

said eustatic composition includes a mild protease and said mild protease includes bromelain.

5. The composition of claim 3 wherein

said polyvalent metal ion includes zinc;

said carbohydrate is a non-toxic saponin glycoside;

said eustatic composition includes a reducing agent and said reducing agent includes ascorbic acid; and

said eustatic composition further includes a mild protease and said mild protease includes bromelain

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6. A eustatic formulation comprising either:

(I) EU-PAN A, which includes

- 5 (a) a glycosaminoglycan comprising at least one member selected from the group consisting of hyaluronic acid and a mixture of hyaluronic acid and sulfated chondroitins;
- 10 (b) a polyvalent ion in an amount suitable for daily administration to an adult human, said polyvalent metal ion comprising at least one member selected from the group consisting of divalent zinc, manganese, iron (the ferrous ion), copper (cuprous) and
- 15 trivalent chromium;
- (c) a reducing agent comprising at least one member selected from the group consisting of ascorbic acid, cysteine and dihydroxymaleate; and
- 20 (d) a mild protease comprising at least one member selected from the group consisting of bromelain and papain.

(II) EU-PAN B, which includes

- 25 (a) a non-toxic saponin glycoside comprising at least one member selected

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from the group consisting of eleutherosides and panaxosides;

- 5 (b) a polyvalent metal ion in amount suitable for daily administration to an adult human, said polyvalent metal ion comprising at least one member selected from the group consisting of divalent zinc, manganese, iron (ferrous), copper (cuprous) and trivalent chromium; and

- 10 (c) a reducing agent consisting of ascorbic acid;

or (III) EU-PAN C, which includes

- 15 (a) a glycosaminoglycan consisting of a mixture of N-acetyl D-glucosamine and D-glucuronic acid;

- 20 (b) a polyvalent metal ion in an amount suitable for daily administration to an adult human, said polyvalent metal ion comprising at least one member selected from the group consisting of divalent zinc, manganese, iron (the ferrous ion), copper (the cuprous ion) and trivalent chromium;
- 25

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(c) a reducing agent comprising at least one member selected from the group consisting of ascorbic acid, cystein and dihydroxymaleate; and

(d) a mild protease comprising at least one member selected from the group consisting of bromelain and papain.

7. The formulation of claim 6 wherein:

EU-PAN A further includes

(e) a supportive base comprising at least one member selected from the group consisting of ribonucleic acid (RNA), inositol, pyridoxine, B-complex, dolomite, superoxide dismutase, and nicotinamide,

EU-PAN B further includes

(d) a mild protease consisting of bromelain, and

(e) a supportive base comprising at least one member selected from the group consisting of ribonucleic acid (RNA), inositol, pyridoxine, B-complex, dolomite, superoxide dismutase and nicotinamide; and

EU-PAN C further includes

- (e) a supportive base comprising at least one member selected from the group consisting of ribonucleic acid (RNA), inositol, pyridoxine, B-complex, dolomite, superoxide dismutase and nicotinamide.

8. The formulation of claim 7 wherein:

the polyvalent metal ion selected for EU-PAN A or EU-PAN B or EU-PAN C includes zinc provided in an amount within the range of 15 mg. to 30 mg. and copper (cuprous) provided in an amount within the range of 1mg. to 2mg.,

the reducing agent selected for EU-PAN A or EU-PAN B or EU-PAN C includes ascorbic acid provided in an amount within the range of 500mg. to 3g., and

the mild protease selected for EU-PAN A or EU-PAN B or EU-PAN C includes bromelain provided in an amount within the range of 50mg. to 150mg.

9. The formulation of claim 8 wherein:

the glycosaminoglycan selected for EU-PAN A is either hyaluronic acid provided in an amount within the range of 500mg. to 10g. or a

mixture of hyaluronic acid and sulfated chondroitins provided in an amount within the range of 500 mg. to 10g.;

5 the non-toxic saponin glycoside selected for EU-PAN B is either eleutherosides provided in an amount within the range of 500mg. to 10g. or panaxosides provided in an amount within the range of 500mg. to 10g; and

10 the mixture of N-acetyl D-glucosamine and D-glucuronic acid of EU-PAN C is provided in an amount within the range of 500mg. to 10g.

10. The formulation of claim 6 wherein:

15 the components (a)-(d) of EU-PAN A or EU-PAN C are mixed with a pseudoaqueous substance comprising one or more members selected from the group consisting of N-methyl pyrrolidinone, ethylene cyclic carbonate and hydrogen peroxide.



European Patent
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EUROPEAN SEARCH REPORT

0066283

Application number

EP 82 10 4734

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 7)
A	FR-A-1 176 917 (AMERICAN HOME PRODUCTS CORPORATION) * Page 4, column 2, abstract III *	1	A 61 K 31/725 A 61 K 45/06
A	US-A-4 058 621 (WILLIAM W. HILL) * Column 14, lines 38-51; claim 1 *	1	
A	EP-A-0 012 115 (CIBA-GEIGY AG) * Page 18, lines 2-6; claim 1 *	1	
A	EP-A-0 000 133 (CIBA-GEIGY AG) * Page 12, lines 2-5; claim 1 *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 7)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 28-08-1982	Examiner BRINKMANN C.	
CATEGORY OF CITED DOCUMENTS			
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T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			